TREATMENT WITH LEVOTHYROXINE DOES NOT NORMALIZE SERUM CHOLESTEROL IN HYPOTHYROID PATIENTS

Hypothyroidism is the second most common endocrine disease affecting approximately 5% of the population, particularly females and older adults (1). Fortunately, the diagnosis and treatment are straightforward for the majority of patients. Both rely on measuring serum levels of thyrotropin (TSH), the pituitary hormone that fluctuates according to the circulating levels of thyroid hormones - thyroxine (T4) and its biologically active metabolite, triiodothyronine (T3). High serum TSH levels indicate that the thyroid secretion is insufficient, establishing the diagnosis of primary hypothyroidism. Standard treatment is with levothyroxine (LT4), the dose of which is adjusted until serum TSH levels have returned to the normal reference range. At this point most patients are asymptomatic and clinically euthyroid (2). However, mounting evidence indicates that normalization of TSH levels might not reflect regularization of all T3-dependent biological effects or that all signs and symptoms of hypothyroidism are eliminated (3). This is an important concept as quantifying the descrepency between tissue thyroid status and serum TSH is key to the management of hypothyroidism .

Recent studies have revealed that the liver might have diminished T3 signaling in euthyroid individuals on LT4 as total- and LDL-cholesterol levels remain higher in LT4-treated patients with normal serum TSH. In keeping with this LT4 treated patients have a higher utilization of statins (3-5). This new information should alert physicians to closely monitor the lipid profile of LT4-treated patients as they are at increased risk of developing hypercholesterolemia, despite having normal serum TSH levels.

Preclinical studies of LT4-treated thyroidectomized rats indicate that plasma and tissue T3 levels are not normalized despite normal serum TSH levels (6). This is associated with reduced T3-signaling in the liver, skeletal muscle and brain (7). In LT4-treated patients, there is strong objective evidence that the liver might remain hypothyroid. The lipid profile of 26 female and 3 male euthyroid patients studied before and one year after total thyroidectomy revealed that while on LT4 therapy patients exhibited an increase in serum LDL-cholesterol levels of 6 mg/dl, despite normalization of serum TSH (5). A similar study of 1,092 LT4-treated female patients also revealed elevation of about 15 mg/dl in total cholesterol levels two years after surgery (4). In fact, a meta-analysis of 65 studies that compared 1,878 LT4-treated patients to 14,493 healthy controls revealed that both total-cholesterol and LDL-cholesterol remain elevated by 9.6 and 3.3 mg/dl, respectively, after serum TSH has been normalized (8). In fact, NHANES data on 360 female and 109 male patients on LT4 as compared to controls matched for age, sex and ethnic background, revealed that patients on LT4 are 54% more likely to be on statins (3).

There is general consensus that T3 acts by modifying the expression of gene sets in virtually every cell. A reduction in T3 signaling modifies the expression of gene sets that are sensitive to T3, explaining the signs and symptoms of hypothyroidism. T3 signaling in the liver sets the balance between cholesterol and bile acid syntheses. A reduction in T3 signaling elevates serum cholesterol levels by slowing down the expression of Cyp7A, the key enzyme in the pathway that converts cholesterol to bile acids. Therefore, the fact that total cholesterol homeostasis is

not restored in LT4-treated patients is a strong indication that T3-signaling in the liver remains abnormally low, despite normalization of serum TSH levels.

As in many tissues, T3 signaling in the liver is defined by the levels of circulating T3. There is general understanding that in LT4-treated patients two deiodinase pathways, D1 and D2, deiodinate T4 and to produce T3, fully restoring circulating and tissue T3 levels (9). However, evidence that this *is not* the case has been available since the early 70s (10). Despite subsequent smaller studies suggesting otherwise (11,12), in a cross-sectional study of 1,811 LT4-treated hypothyroid patients with normal serum TSH, serum T3 was found to be 17% lower when compared to 3,875 control individuals; in 15.2% of the patients, serum T3 is below the normal range (13). Similar findings were obtained in 135 consecutive patients who underwent total thyroidectomy (14), and through the analyzes of publicly available NHANES data on 469 LT4-treated patients (3).

It is notable that in some of these studies, normalization of serum cholesterol was achieved by increasing the dose of LT4 (4,5), a change that also normalizes serum T3 but results in lowering serum TSH below the normal reference range. Future clinical trials will be necessary to determine whether the long-term benefits of restoring cholesterol homeostasis outweighs the risks of keeping a serum TSH below normal range. An alternative possibility is to place hypothyroid patients on combination therapy, what results in slightly higher serum T3. However, this regimen is controversial and has not been accepted for routine treatment of hypothyroidism (2).

It is also important to recognize that the slightly lower serum T3 levels observed in LT4-treated patients cannot be categorized as subclinical hypothyroidism. The latter is a condition in which patients exhibit mildly elevated serum TSH while keeping serum T4 and T3 levels within the population reference range. Whereas such patients do exhibit alterations in lipid profile, it is not clear that treatment with LT4 results in measurable benefits . Indeed, it is only in the more severe end of SCH that clear benefits of correcting SCH with regard to cardiovascular risk factors are seen and only in younger and middle-aged individuals (15). Persistent subclinical hypothyroidism due to ongoing thyroid inflammation or other intrinsic thyroid disease, will result in preservation of T3 levels and T3:T4 ratio which is not observed in individuals on LT4.

Conclusion:

This summary highlights that whilst abnormal lipid profiles and hypothyroidism often promote screening for the other condition, it is important to realise that individuals on LT4 are also at increased risk of developing hyperlipidemia. Therefore the screening for an abnormal lipid profile should continue in hypothyroid individuals even after normalization of TSH. This summary also raises a broader issue; lipid metabolism is something which we can readily measure with simple blood tests it is easy to identify as a problem. The effects of lower T3 availability and subsequent gene expression in other tissues such as the brain, may affect outcomes such as fatigue and mood which are less easily measured but of perhaps greater importance to the patient.

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